

We claim:

1. A hydrophilic matrix formulation suitable for once-a-day administration comprising:
  - a. divalproex sodium, and;
  - 5 b. said divalproex sodium is in admixture with a sufficient quantity of a pharmaceutically acceptable polymer, so that said formulation exhibits the following in-vitro dissolution profile, when measured in a type 2 dissolution apparatus (paddle) at 100 rpm, at a temperature of  $37 \pm 0.5$  C, in 500ml of 0.1N HCl for 45 minutes, followed by 900ml of 0.05M phosphate buffer containing 75 mM sodium laurel sulfate ( pH5.5) for the remainder of the testing period:
    - i. no more than about 30 % of total valproate is released after 3 hours of measurement in said apparatus;
    - ii. from about 40 to about 70% of total valproate is released after 9 hours of measurement in said apparatus;
    - 15 iii. from about 55 to about 95% of total valproate is released after 12 hour of measurement in said apparatus, and;
    - iv. not less than 85% of total valproate is released after 18 hours of measurement in said apparatus.
2. The formulation according to claim 1 in which said formulation exhibits the following in-vitro dissolution profile:
  - i. from about 15% to about 30% of total valproate is released after 3 hours of measurement in said apparatus;
  - ii. from about 40% to about 70% of total valproate is released after 9 hours of measurement in said apparatus;
  - 25 iii. from about 55% to about 90% of total valproate is released after 12 hours of measurement in said apparatus, and;
  - iv. not less than 88% of total valproate is released after 18 hours of measurement in said apparatus.

3. The formulation according to claim 1 in which said formulation exhibits the following in-vitro dissolution profile:
- i. from about 15% to about 27% of total valproate is released after 3 hours of measurement in said apparatus;
  - 5 ii. from about 44% to about 69% of total valproate is released after 9 hours of measurement in said apparatus;
  - iii. from about 59% to about 90% of total valproate is released after 12 hours of measurement in said apparatus, and ;
  - 10 iv. not less than 88% of total valproate is released after 18 hours of measurement in said apparatus.
4. The formulation according to claim 1 in which said divalproex sodium is present in the amount of from about 40 to about 80w/w% based upon the total weight of the formulation.
5. The formulation according to claim 3 in which said polymer is a water soluble
- 15 hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and mixtures thereof.
6. The formulation according to claim 5 in which said divalproex sodium is present in the
- 20 amount of from about 45 to about 65 w/w%, based upon the total weight of the formulation.
7. The formulation according to claim 6 in which said polymer is present in the amount of from about 20 to about 50 w/w%, based upon the total weight of the formulation.
8. The formulation according to claim 7 which further comprises one or more
- 25 pharmaceutically acceptable excipients.
9. A method for treating migraine comprising administering a formulation according to claim 1 to a patient in need thereof.
10. A method for treating epilepsy comprising administering a formulation according to claim 1 to a patient in need thereof.

11. A method for treating bipolar disorders comprising administering a formulation according to claim 1 to a patient in need thereof.
12. The formulation according to claim 1, which when ingested orally produces a  $C_{\max}$  that is statistically significantly lower than the  $C_{\max}$  produced by a delayed release divalproex sodium tablet, when each is determined at steady state in a fasting population.
13. The formulation according to claim 12 which:
- produces a  $C_{\min}$  that is not statistically significantly different from the  $C_{\min}$  produced by said delayed release divalproex sodium tablet, when each is determined at steady state in a fasting population, and;
  - said formulation produces an AUC value that is equivalent to the AUC value generated by said divalproex sodium delayed release tablet, when each is determined at steady state in a fasting population.
14. A hydrophilic matrix formulation suitable for once-a-day administration comprising:
- divalproex sodium, and;
  - said divalproex sodium is in admixture with a sufficient quantity of a pharmaceutically acceptable polymer, so that said formulation exhibits the following in-vitro dissolution profile, when measured in a type 2 dissolution apparatus (paddle) at 100 rpm, at a temperature of  $37 \pm 0.5$  C, in 500ml of 0.1N HCl for 45 minutes, followed by 900ml of 0.05M phosphate buffer containing 75 mM sodium laurel sulfate (pH5.5) for the remainder of the testing period:
    - from about 15% to about 27% of total valproate is released after 3 hours of measurement in said apparatus;
    - from about 44% to about 69% of total valproate is released after 9 hours of measurement in said apparatus;
    - from about 59% to about 90% of total valproate is released after 12 hours of measurement in said apparatus, and;
    - not less than 88% of total valproate is released after 18 hours of measurement in said apparatus.

15. The formulation according to claim 14, which when ingested orally produces a  $C_{\max}$  that is statistically significantly lower than the  $C_{\max}$  produced by a delayed release divalproex sodium tablet, when each is determined at steady state in a fasting population.

5 16. A hydrophilic matrix formulation suitable for once-a-day administration comprising:

- a) a valproate compound, and;
- b) said valproate compound is in admixture with a sufficient quantity of a pharmaceutically acceptable polymer, so that said formulation exhibits the following in-vitro dissolution profile, when measured in a type 2 dissolution apparatus (paddle) at 100 rpm, at a temperature of  $37 \pm 0.5^{\circ}\text{C}$ , in 500ml of 0.1N HCl for 45 minutes, followed by 900ml of 0.05M phosphate buffer containing 75 mM sodium laurel sulfate, pH5.5, for the remainder of the testing period:

- 15 i. no more than about 30 % of total valproate is released after 3 hours of measurement in said apparatus;
- ii. from about 40 to about 70% of total valproate is released after 9 hours of measurement in said apparatus;
- 20 iii. from about 55 to about 95% of total valproate is released after 12 hour of measurement in said apparatus, and;
- iv. not less than 85% of total valproate is released after 18 hours of measurement in said apparatus.

17. The formulation according to claim 1 in which said formulation exhibits the following in-vitro dissolution pattern:

- 25 i. from about 15% to about 30% of total valproate is released after 3 hours of measurement in said apparatus;
- ii. from about 40% to about 70% of total valproate is released after 9 hours of measurement in said apparatus
- 30 iii. from about 55% to about 90% of total valproate is released after 12 hours of measurement in said apparatus

- iv. not less than 88% of total valproate is released after 18 hours of measurement in said apparatus.

18. The formulation according to claim 1 in which said formulation exhibits the following in-vitro dissolution pattern:

- 5                   i. from about 15% to about 27% of total valproate is released after 3 hours of measurement in said apparatus;
- ii. from about 44% to about 69% of total valproate is released after 9 hours of measurement in said apparatus
- iii. from about 59% to about 90% of total valproate is released after 12 hours of measurement in said apparatus
- 10                  iv. not less than 88% of total valproate is released after 18 hours of measurement in said apparatus.

- 15           19. A method for the treatment of epilepsy in a patient in need thereof comprising:
  - a) the administration of a single daily dose of at least one divalproex sodium formulation according to claim 1 in which said daily dose is from 5% to 35% greater than the corresponding total daily dose that would be required for the patient consuming a delayed release divalproex sodium tablet, and;

- 20           b) when said formulation is ingested orally said formulation produces:
  - i) a  $C_{\max}$  that is statistically significantly lower than the  $C_{\max}$  produced by the delayed release divalproex sodium tablet, when each is determined at steady state in a fasting population,
  - ii) a  $C_{\min}$  that is statistically significantly higher than the  $C_{\min}$  produced by said
  - 25   delayed release divalproex sodium tablet, when each  $C_{\min}$  is determined at steady state in a fasting population;
  - iii) an AUC value that is equivalent to the AUC value generated by said divalproex sodium delayed release tablet, when each AUC is determined at steady state in a fasting population;

- c) with the proviso that the pharmacokinetic comparison in (b) is based upon total daily doses that differ by a factor of from 5 to 30%, when compared on a milligram to milligram basis.
20. The method according to claim 22 in which the total daily dose of said formulation is about 10% greater than the total daily dose of said delayed release divaproex sodium tablet.
21. The method according to claim 19 in which said patient consumes a formulation according to claim 13.

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